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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,503	12/20/2004	Hans-Michael Eggenweiler	MERCK-2957	7857

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,503	EGGENWEILER ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31 and 32* is/are allowed.

6)☒ Claim(s) *1-15,18 and 21* is/are rejected.

7)☒ Claim(s) *16,17 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Request for Continuing Examination

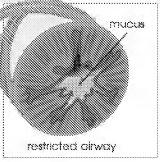
A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but before decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) was timely paid, the appeal is withdrawn pursuant to 37 CFR 1.114 and prosecution in this application is reopened pursuant to 37 CFR 1.114. Applicant's submissions filed 04-10-2008 and 01-12-2009 are entered.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treatment of asthma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The present specification offers insufficient evidence that the claimed methods treat specific diseases/conditions susceptible to PDE-4 inhibition amelioration,



although the claims encompass treatment of such diseases/conditions. The following reasons apply to this enablement rejection.

Pursuant to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue;" see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the methods.

The scope of the methods is the use of the trillions of thiazole compounds comprehended under formula I.

(b) Scope of the diseases covered.

Asthma is a disease of the lungs that affects bronchial tubes or airways; a reversible obstructive airway disease. Unlike other conditions that obstruct airways, such as cystic fibrosis, chronic bronchitis and emphysema, asthma does not affect sufferers all the time. During an asthma attack, membranes inside bronchial tubes release mucus and become inflamed, causing muscles to contract and create wheezing spasms. Attacks can be severe or relatively mild, but the condition is

dangerous and can easily spiral out of control. Specific causes of asthma are far from straightforward. Asthma is divided into a number of different types:

- **Allergic Asthma:** Triggered by allergens, e.g., pet dander, pollen, dust mites, pollutants, wood dust, smoke, irritants, chemicals, viral infections, bacteria, stress, emotion, exercise.
- **Childhood Allergic Asthma:** Maternal smoking can contribute to asthma or other infant lung function impairment, even before a child is born. Continued exposure to cigarette smoking can irritate the respiratory tract, making infants and children particularly vulnerable to allergic asthma.
- **Intrinsic Asthma:** Allergies do not play a part; its typical onset occurs after age 40. Possible causes include respiratory irritants, e.g., perfumes, cleaning agents, fumes, smoke, cold air, upper respiratory infections, gastroesophageal reflux. Intrinsic asthma tends to be less responsive to treatment than allergic asthma.
- **Exercise-Induced Asthma:** Can affect anyone at any age and may be attributed to loss of heat and moisture in the lungs with strenuous exercise. Frequent coughing during exercise may be the only symptom, but exercise-induced asthma symptoms can be more severe in cold, dry conditions. Prophylactic medications can prevent onset of asthmatic symptoms for sensitive individuals.
- **Nocturnal Asthma:** Affects people during sleep, regardless of time of sleep. Symptoms can be triggered by allergens in bedding or bedroom, decrease in room temperature and gastroesophageal reflux.

- **Occupational Asthma:** Occurs as a result of breathing chemical fumes, wood dust, or other irritants over long periods of time.
- **Steroid-Resistant Asthma:** Overuse of asthma medications can lead to status asthmaticus, a severe asthma attack that fails to respond to medication and may require mechanical ventilation.

The claimed scope includes treating all forms of asthma, which are inadequately enabled based on PDE-4 inhibition. The Formula (I) compounds are disclosed to inhibit PDE-4 and the specification hypothesizes these compounds are therefore useful to treat all forms of asthma noted above for which Appellants provide insufficient competent evidence. Further, Appellants have not provided sufficient competent evidence that the instantly disclosed tests (pages 21-28, *inter alia*) are highly predictive for all forms of asthma disclosed and embraced by the claim language for the intended host.

(2) The nature of the invention and predictability in the art:

The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance:

The direction and guidance provided is very limited. The dosage range information (page 83+, *inter alia*) is vague and meager. Even the broadest range is 25 fold. Moreover, this dosage information is generic, the same for the many disorders covered by the specification. There is no specific direction or guidance regarding a

therapeutic regimen or dosage effective specifically for various compounds described for various medical conditions comprehended.

In *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 86 USPQ2d 1196, 1202 (Fed. Cir. 2008), Mylan Labs. challenged the enablement of an Ortho-McNeil Pharm. patent. J. Rader noted three specific informative instances of the enabling teachings of the Ortho-McNeil patent there at issue:

> [1] ...the average adult requires 30-2000 milligrams of the claimed compounds administered in two to four doses of 10-500 milligrams. [2] The specification also teaches a skilled artisan to use the claimed compounds in a manner similar to the drug phenytoin. [3] Further the specification directs the reader to a reference by L.S. Goodman, which teaches that after establishment of a low initial dose, the dosage is increased at appropriate intervals as required for control of seizures or as limited by toxicity with further adjustments according to plasma drug concentrations. ...

(Numbering added.) Such types of information are completely lacking in this specification. Moreover, the dosage is generic; the same for the many asthma disorders covered by the claims. The claims cover seven different types of asthma and the specification fails to provide the information, approvingly noted by J. Rader, for the present methods in regard to these conditions. *Ortho-McNeil* supports this rejection for lack of enablement.

(4) State of the Prior Art:

Lu, et al. Respiratory Medicine, 2009, Jan. 7, in press, <http://www.leaddiscovery.co.uk/articles/19135348/dailyupdate>, downloaded 3/8/2009, reports, "Over a 14-day treatment period, the oral PDE4 inhibitor MK-0359 improved

lower airway function, symptoms and rescue medication use in chronic asthma, although at the expense of gastrointestinal adverse experiences."

Giembycz, *Brit. J. Pharmacology* (2008) 155, 288–290, cautiously remarks:

> It is clear that many compounds still in development may not reach the market as a monotherapy unless their emetic liability has been reduced. In this respect, data arising from the oglemilast and tetomilast clinical development programmes are awaited with much interest. However, even if the therapeutic ratio of these compounds has been improved, they still may not achieve the prominence in asthma and COPD treatment initially predicted.

APM Health Europe, dated May 21, 2007, <http://health.apmnews.com/story.php?mots=ICOS&searchScope=1&searchType=0&numero=L6764>, downloaded 3/8/2009, reports:

> "Pfizer's phosphodiesterase 4 (PDE4) inhibitor tofimilast was not found to be effective in asthma or chronic obstructive pulmonary disease in two phase II trials presented at the American Thoracic Society conference in San Francisco. …
>
> At the end of the six-week study, the primary endpoint of forced expiratory volume in one second (FEV1) before bronchodilator use was not significantly different in the tofimilast and placebo groups, the study abstract says.
>
> Tofimilast was also no better than placebo on secondary endpoints such as symptoms, bronchodilator use, dyspnea and quality of life. …
>
> Tofimilast was not found to be effective at any dose either in COPD or in asthma, the researchers concluded.

Barnart, et al., Life Sci. 2007 Proc Life Sci., PC124, http://www.physoc.org/custom2/publications/proceedings/archive/article.asp?ID=Proc%20Life%20SciencesPC124, downloaded 3/8/2009, states, "Inhibitors of … PDE4 developed to treat asthma and COPD have so far met with limited clinical success, often due to gastrointestinal side-effects."

(5) Working Examples:

Examples 1-7 show production of a meager number of compounds from among the trillions covered by Formula I. No *in vivo* biological data is presented. *In vitro* testing is shown only for inhibition of proliferation of T-cells (Example I) and control of cytokine production in human PBMCs (Example II). The working examples do not show formation of pharmaceutically acceptable salts or stereoisomers of compounds of Formula I, which are encompassed by the method claims. Regarding such salts and stereoisomers, *Morton Intrntl. v. Cardinal Chem.*, 28 USPQ2d 1190, 1194 (Fed. Cir. 1993) stated:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ...

(6) Skill of those in the art: The discussions by Lu, Giembycz, APM Health Europe and Barnart substantiate the need for further inventive research in order to be able to use the present methods to treat all asthma forms.

(7) The quantity of experimentation needed:

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding testing types needed to support *in vivo* use. MPEP 2163, *et. seq.* The application disclosure is insufficient to enable instantly claimed methods based solely on disclosure of inhibition of proliferation of T-cells (Example I) and control of cytokine production in human PBMCs (Example II) by Formula (I) compounds. Such experimentation is potentially open-ended.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Sitrick v. Dreamworks LLC, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable all of the embodiments. "Because the asserted claims are broad enough to cover both [embodiments], the [specification] must enable both embodiments." Here, the claims at issue cover treating many forms of asthma and do not enable all of them.

Automotive Tech. Int'l. v. BMW of N. America, Inc., 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one of the embodiments. "Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both [embodiments], which the specification fails to do." Here, the claims at issue cover treating many forms of asthma and do not enable all of them.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, in the definition of R3 and R3', in each of the last two recited moieties, the nitrogen atom has only two valences. In the definition of R7, in each of the 10th and 11th recited moieties, the nitrogen atom has only two valences. If Het is an aromatic heterocyclic ring, it cannot be substituted by carbonyl oxygen.

In claim 18, process a), it is not possible to determine whether "any [protected] further OH and/or amino group present" is on a compound of formula I, II or III. In claim 18, process b) "converting one or more radicals R1, R2, R3 and/or B in a compound of the formula I into one or more radicals R1, R2, R3 and/or B" defines no process at all, because no conversion takes place. In claim 18, process b) further defines no process at all, because it fails to define the intended procedures and/or reactants involved. Claim 18, process c) is ungrammatical in the recitation "converting a basic compound ... is converted." An "acid" fails to particularly point out and distinctly claim the subject matter, because acid is inclusive of many compounds which may be variously defined:

- **Arrhenius acid**: a substance that increases the concentration of hydronium ion when dissolved in water. This definition limits acids to substances that can dissolve in water.
- **Brønsted-Lowry acid**: a proton donor.
- **Lewis acid**: an electron-pair acceptor.

Potential Duplicate Claim

Applicant is advised that should claim 1 be found allowable, claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two

claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 17 is an essential duplicate of claim 1, because it adds nothing to distinguish over claim 1.

If applicants intend that only certain compounds of formula I are phosphodiesterase IV inhibitors, then claim 17 would be rejectable under 35 USC 112, paragraph 2, for failure to identify how the phosphodiesterase IV inhibitors of claim 1 are to be distinguished from all compounds of formula I.

Objected Claim – Allowable Subject Matter

Claim 16 and 19 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all limitations of the base claim and any intervening claims. An examiner's statement of reasons for indicating allowable subject matter can be found in the Office Action of 01-11-2008.

Allowed Claims

Claims 31 and 32 are allowed. An examiner's statement of reasons for indicating allowed claims can be found in the Office Action of 01-11-2008.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

Cecilia M. Jaisle